American Journal of Medical Genetics 63:277–289 (1996)

Dubowitz Syndrome: Review of 141 Cases Including 36 Previously Unreported Patients

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We review clinical information on 141 individuals with Dubowitz syndrome, 105 reported since 1965, and 36 previously unreported. We define the Dubowitz syndrome phenotype on the basis of clinical descriptions. The facial appearance is characteristic and present in most patients with Dubowitz syndrome. The phenotypic spectrum is quite variable and ranges from normal growth and head circumference with mild psychomotor retardation and lack of eczema to a condition of severe growth retardation, mental retardation, microcephaly, and eczema. Overall, the condition may involve the cutaneous, ocular, dental, digestive, musculoskeletal, urogenital, cardiovascular, neurological, hematological, and immune systems. Characteristic behavior patterns which have not been cited previously are present in our cases; most patients are hyperactive, shy, hate crowds, and like music, rhythm, and vibrations from music speakers, tape recorders, or transmitted through floors. Dubowitz syndrome is an autosomal recessive disorder with possibly increased frequency of parental consanguinity. Heterogeneity cannot be excluded at this time. © 1996 Wiley-Liss, Inc.

KEY WORDS: Dubowitz syndrome, growth retardation, developmental retardation, eczema, multiple anomalies, aplastic anemia, leukemia

INTRODUCTION

In 1965 Dubowitz described a 13-month-old girl with intrauterine growth retardation, primordial short stature, microcephaly, unusual facial appearance, skin eruptions, and mild mental retardation; her elder sister who died at 3 months also had had intrauterine growth retardation and webbing of the toes, but no skin rash. Grosse et al. [1971] and Opitz et al. [1973] subsequently defined the condition and proposed the designation Dubowitz syndrome.

The syndrome is defined as a condition of pre- and post-natal growth retardation, microcephaly, mild to moderate mental retardation, and eczema. The patients are often hyperactive with short attention span. Facial appearance is characteristic with high or sloping forehead, flat supraorbital ridge, scanty lateral eyebrows, short palpebral fissures, ptosis, abnormally modeled ears, broad and flat nasal bridge, and unusual configuration of the mouth. Genital abnormalities include hypospadias and cryptorchidism. Affected individuals may also have a sacral dimple, clinodactyly of the 5th fingers, and cutaneous syndactyly of the 2nd and 3rd toes. The condition appears to be an autosomal recessive trait. To date, 105 patients with this condition have been reported in 46 publications [in chronologic order: Dubowitz, 1965; Grosse et al., 1971; Opitz et al., 1973; Majewski et al., 1975; Sauer and Spelger, 1977; Borkenstein and Falk, 1978; Wilroy et al., 1978; Fryns et al., 1979; Parrish and Wilroy, 1980; Orrison et al., 1980; Stoll et al., 1980; Walter, 1980; Castro-Gago et al., 1981; Acuña-G et al., 1981; Gröbe, 1983; Nöll-Gröne and Fuhrmann, 1983; Moller and Gorlin, 1985; Walters and Desposito, 1985; Wilhelm and Méhes, 1986; Winter, 1986; Küster and Majewski, 1986; Shuper et al., 1986; Berthold et al., 1987; Chrzanowska and Krajewska-Walasek, 1987; Guarniere et al., 1987; Kondo et al., 1987; Levin et al., 1987; Belohradsky et al., 1988; De los Cobos-Villaseñor, 1988; Weiss et al., 1988; Hochreutener et al., 1990; Lerman-Sagie et al., 1990; Vieluf et al., 1990; Ilyina and Lurie, 1990; Méhes, 1990; Bodemer et al., 1991; Kukushkina et al., 1990; Mathieu et al., 1991; Thuret et al., 1991; Lyonnet et al., 1992; Benso et al., 1992; Gomirato et al., 1992; Dumic et al., 1994; Paradisi et al., 1994; Hansen et al., 1995].

Here we describe 36 previously unreported patients and review the 105 published cases.

Received for publication October 3, 1995; revision received January 12, 1996.

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Dedicated to Jürgen W. Spranger on the occasion of his 65th birthday with admiration and best wishes.

MATERIALS AND METHODS

We were consulted on 45 patients for Dubowitz syndrome between April 7, 1982 and December 24, 1995. All, except for a recent Japanese child, were referred to and evaluated by one of us (J.M.O). These patients were referred by physicians for suspected Dubowitz syndrome, peculiar face, multiple congenital anomalies, or by parents of children known to have Dubowitz syndrome. These patients were examined clinically or through evaluation of history and photos. Of these 45 patients, 36 were diagnosed with Dubowitz syndrome, 5 were possible cases but a definite diagnosis of Dubowitz syndrome was not made; 3 probably did not have Dubowitz syndrome, and 1 case lacked essential clinical information. Thus, 36 patients with an evident diagnosis of the Dubowitz syndrome were included in this study. Of these 36 patients, 27 were referred from the United States, 3 from England, 2 from Canada, and 1 each from Germany, the Netherlands, Brazil, and Japan. Questionnaire data provided by the Dubowitz Syndrome Parent Support Group were available for analysis in 11 of 36 patients. We developed questionnaire data on ten additional patients (Appendix B).

Together with our 36, we reviewed 105 reported patients from 89 families. Of these 105 patients from 46 publications, 9 were reported twice. They include: The original case (A.R.) reported by Dubowitz [1965] and updated by Grosse et al. from information provided subsequently by Victor Dubowitz [1971]; two sibs (J.C. and D.C.) by Opitz et al. [1973] and Walters and Desposito [1986]; B.Z. by Opitz et al. [1973] and Gröbe [1983]; two sibs (B.M. and K.M.) by Grosse et al. [1971] and Moller and Gorlin [1985]; D.B. by Nöll-Gröne and Fuhrmann [1983] and Berthold et al.[1987]; "Vincent" by Bodemer et al. [1991] and Lyonnet et al. [1992]; J.H. by Grosse et al. [1971] and Hansen et al. [1995].

The case reported as "Seckel syndrome" by Müller et al. [1978] may have the Dubowitz syndrome and is included in the analysis.

RESULTS

Identified reasons for referral in the newly reported cases included failure to thrive (6 cases); peculiar face (6); short stature (3); multiple congenital anomalies (2), growth retardation (2); psychomotor retardation (1); vomiting (1); acute exacerbation of long standing skin lesions (1), syndactyly of toes (1), and microcephaly (1).

Sex

This report brings the total of known cases to 141 in 125 families (Table I); 69 of the patients were male, 63 female, and 9 of unknown sex.

Age

The mean age of 109 patients at last visit was 5.3 years, ranging from 1.5 months to 30 years; 137 of 141 patients were still alive. Four patients died of malignant or hematological disorders.

TABLE I. Clinical Manifestations of 105 Reported and 36 Current Cases*

	Reported cases	Present cases	Total cases
Sex	M;48 F;48 ?;9	M;21 F;15	M;69 F;63 ?;9
Mean age (years)	4.7 (1.5/12–30)	7.9 (11/12–18)	5.3 (1.5/12–30)
Mean maternal age (years)	25.8	27.6	26.0
Mean paternal age (years)	29.2	32.0	29.9
Pregnancy			
Gestational age (weeks)	38.5 (27–43)	37.4 (28–42)	38.0 (27–43)
Complication	9	11	20
Poor fetal movement	0	11	11
Delivery			
C-section	8	9	17
Breech	1	1	2
Occiput-posterior	3	0	3
Birth			
Mean weight (g)	2291	2357	2331
Male	2368(1,150–3,600)	2514 (900–3,515)	2413 (900–3,600)
Female	2217(1,300–3,500)	2175(1,445–3,401)	2221(1300–3,500)
Mean length (cm)	45.0	45.1	45.0
Mean OFC (cm)	30.8	31.7	31.0
Prenatal growth retardation[a]	62/88	21/33	83/121
Postnatal growth retardation	87/103	32/36	119/139
Psychomotor retardation	66/89	24/36	90/125
Neonatal			
Respiratory problems	17	4	21
Feeding difficulties	16	17	33

*Parentheses indicates the range observed.
[a]Birth weight is less than 2,500 g at term.

Race

The Dubowitz syndrome was observed in the United States (49 cases), Germany (27), and Russia (23), and less frequently in England (9), France (9), Italy (4), Hungary (4), Spain (2), Israel (2), Mexico (2), Canada (2), Japan (2), Belgium (1), Poland (1), Croatia (1), The Netherlands (1), Venezuela (1), and Brazil (1); thus, this condition seems to be worldwide in occurrence.

Family History

In the family reported by Grosse et al. [1971] asthma and/or hay fever occurred in three generations. The family reported by Sauer and Spelger [1977] included 4 individuals with malignancy, speech defect (2) and allergy (2) in four generations, and an apparently unaffected brother with cryptorchidism, eczema, and speech defect. Orrison et al. [1980] reported migraine in the maternal grandmother and an aunt, and microcephaly, anisocoria, and webbed toes in the maternal grandmother. A mother of one of our cases (L.J.) also had migraine headaches. In the cases reported by Walter [1980] the mother had microcephaly and short stature; a maternal aunt had porencephaly; a daughter of a paternal uncle had hypertelorism, epicanthus, polydactyly, eczema, absence of lateral incisors; two sibs born to a paternal aunt had hypertelorism, flat nose, low-set, large ears, microcephaly, sparse hair, hypoplastic zygomata, micrognathia, and scanty eyebrows. Familial short stature was reported by Nöll-Gröne and Fuhrmann [1983]. Levin et al. [1987] reported on a family in which both maternal and paternal cousins had isolated cleft palate, and a maternal cousin had mental retardation. In the family reported by Guarniere et al. [1987], the father and the sister of the patient had severe myopia. The father of the patient reported by Kukushkina et al. [1990] had short stature and microcephaly. Benso et al. [1992] reported on a maternal cousin with cutaneous syndactyly of the 2nd and 3rd toes. Given the vagaries of ascertainment biases, it is difficult to decide whether any of these is of genetic importance.

Prenatal History

A specific association of prenatal exposure to teratogenic agents has not been described. Diverse exposures include heroin and LSD during the first trimester [Opitz et al., 1973], alcohol and 30 cigarettes/day [Küster and Majewski, 1986], 10 cigarettes/day [Hochreutener et al., 1990], and lead during pregnancy [Walter, 1980]. The mother of our case L.B. was reported to be a "heavy smoker." One mother was treated for hypothyroidism [Opitz et al., 1973]; another took an unknown amount of vitamin E at 7 and 20 weeks of gestation [Kukushkina et al., 1990].

Pregnancy History

Pregnancy was complicated in 20 mothers, including bleeding (spotting, 4 cases), urogenital infection (3), inadequate maternal weight gain (2), hyperemesis gravidarum (2), polyhydramnios (2), oligohydramnios (2), hypertension (1), preeclampsia (1), toxemia (1), edema (1), abruptio placentae (1), and placenta previa (1). EPH-gestosis was reported by Küster and Majewski [1986]. Paucity of fetal movement was noted in 11 cases and excessive movement in one [Grosse et al., 1971]. Mean gestational age at birth was 38 weeks, ranging from 27 to 43 weeks. Fifteen of one hundred fourteen cases (13.1%) were delivered prematurely (prior to 36 weeks).

Delivery

Seventeen children were born by caesarean section because of fetal distress (4 cases), placental insufficiency (3), narrow pelvis (2), placental dystrophy (1), toxemia (1), preeclampsia (1), or breech presentation (1). Two patients were born from a breech presentation [Borkenstein and Falk, 1978; our case N.C.]. Occiput-posterior presentation was noted in three cases [Müller et al., 1978; Walter, 1980]. Abnormal findings at delivery included discolored amniotic fluid [Müller et al., 1978], unspecified anomaly of the umbilical cord and placenta [Opitz et al., 1973], shrivelled placenta [Wilhelm and Méhes, 1986], small placenta [Müller et al., 1978], umbilical cord loop [Castro-Gago et al., 1981], umbilical cord around the neck [Kukushkina et al., 1990], very short umbilical cord [Wilroy et al., 1978], and calcified placenta (our case M.L.).

Birth Data

The average birth weight of males was 2,413 g (range 900–3,600 g) and 2,221 g for females (range 1,300–3,500 g). Intrauterine growth retardation (birth weight less than 2,500 g at term) was characteristic and noted in 83/121 patients (68.6%). Birth length averaged 45.0 cm, and average occipitofrontal circumference (OFC) was 31.0 cm. Average maternal age was 26.0 and paternal age 29.9 years at the child's birth.

Neonatal Problems

Neonatal problems included respiratory (21 cases) and feeding difficulties (33 cases) with associated later failure to thrive. Respiratory problems included tachypnea, stridor, respiratory distress, rhinorrhea, and pneumothorax. Some of the patients required resuscitation. Feeding difficulties included poor suck, vomiting and gastro-esophageal reflux proven in five cases [Mathieu et al., 1991; our cases B.B., R.H.]. Hiatal hernia was noted in one patient [Mathieu et al., 1991]. Naso-esophageal tube feeding was used occasionally. In one of our cases (R.H.), gastrostomy was performed because of severe gastro-esophageal reflux. Jaundice requiring phototherapy or blood transfusion was noted in two children [Stoll et al., 1980; our case E.S.]. Convulsions were reported in one case [Wilroy et al., 1978].

Growth and Development

Growth. Postnatal growth retardation was noted in 119/139 patients (85.6%). Fourteen patients were born without intrauterine growth retardation, but subsequently their growth became severely retarded [Wilroy et al., case 7, 1978; Orrison et al., case 5, 1980; Hochreutener et al., 1983; Chrzanowska and Krajewska-Walasek, 1987; Levin et al., 1987; Lyonnet et al., 1992; our eight cases B., H.C., T.H., C.K., J.L., M.N.,

K.T., and J.H.]. Patients born with a normal birth weight tended to be microcephalic and to develop postnatal growth retardation. On the other hand, two cases reported by Mathieu et al. [1991] had intrauterine growth retardation, but thereafter manifested normal growth except for severe microcephaly. Our case (J.A.) had severe intrauterine growth retardation (birth weight 1,000 g; length 29.2 cm), but then his growth improved to the point where he weighed 35.8 kg (50th centile for chronological age) and was 137 cm tall (10–25th centile for chronological age) at age 11 years. He had a characteristic facial appearance, sparse hair, very dry and rough skin, flat feet, crowded toes, poor feeding and severe vomiting with constipation, cryptorchidism, asthma, hearing loss, frequent ear infections, and mild psychomotor retardation with some expressive language delay. Two of our cases (B.B. and J.F.) had neither intrauterine nor postnatal growth retardation. B.B. had characteristic facial appearance, mild microcephaly, neonatal apneic spells, gastro-esophageal reflux, hypotonia, "milk allergy," recurrent ear and sinus infections, and mild psychomotor delay. She had failure to thrive during infancy, but subsequently was at the 80th–85th centile on growth charts for height and weight. J.F. had a characteristic facial appearance, hypospadias, and mild psychomotor delay with some expressive language delay (Appendix A, Fig. 1).

Normal [Lyonnet et al., 1992] and early [our case J.H.] pubertal status in two males, and regular heavy menarche beginning at age 13 years were reported [Hansen et al., 1995].

Fig. 1. J.F. at age 2½ years.

Psychomotor development. The level of intellectual functioning ranged from severe mental retardation to average intelligence. Psychomotor retardation was noted in 90 of 125 cases (72%). Of these 90 cases, mild, moderate, and severe mental retardation were noted in 46 (51.1%), 13 (14.4%), and 9 cases (10%), respectively. Indeed, one half of the children had low average or average intelligence as reported by Parrish and Wilroy [1980]. In the other 22 cases the degree of mental retardation was not mentioned. In patients with normal I.Q., a delay in development of self-help skills was noted by Parrish and Wilroy [1980]. Most of the mentally retarded patients in our cases needed special educational attention, and attended special education class or special school. Speech delay was noted in 24/36 of our cases.

CLINICAL MANIFESTATIONS

Table II summarizes clinical characteristics of patients with the Dubowitz syndrome.

TABLE II. Main Clinical Manifestations

	Reported cases	Present cases	Total cases
Craniofacial			
Microcephaly	85	27	112
High (sloping) forehead	39	4	43
Blepharophimosis	41	19	60
Ptosis	35	18	53
Broad nasal bridge	29	2	31
Prominent round tip	3	17	20
Flat nasal bridge	12	4	16
Low-set ears	18	6	24
Posteriorly angulated ears	11	4	15
Large mouth	14	2	16
High (narrow) palate	21	9	30
Cleft palate	9	13	22
Micrognathia	66	15	81
Ocular problems	18	13	31
Tooth problems	29	12	41
Skin			
Sparse (thin) hair	44	14	58
Eczema	39	20	59
G-I tract			
Feeding difficulties	14	17	31
Vomiting	14	10	24
Chronic diarrhea	13	2	15
Skeletal			
Clinodactyly of 5th fingers	33	14	48
Cutaneous syndactyly (toes 2 and 3)	14	8	22
Club foot	8	3	11
Hyperextensible joints	8	5	13
Sacral dimple	6	4	10
Retarded bone maturation	30	7	37
Congenital heart defects	8	5	13
Urogenital			
Cryptorchidism	16	10	26
Hypospadias	7	3	10
Neurological problems	17	8	25
Seizures	8	5	13
Behavior			
High-pitched voice	31	7	38
Hyperactivity	37	13	50
Frequent infections	27	18	45
Allergy	7	15	22
History of operation	15	18	33

Craniofacial Manifestations

Facial anomalies are perhaps the most diagnostic of all physical signs. Parentheses indicate the number of cases in which the anomaly was seen.

Skull. Microcephaly was present in 112 patients; normal OFC was noted in two cases. Also noted were triangular face (12), facial asymmetry and/or weakness (9), craniosynostosis (5), narrow bifrontal diameter (5), dolichocephaly (4), trigonocephaly (4), small face (4), narrow face (3), brachycephaly (3), large open fontanelle (2), prominent occiput (2), flat occiput (1), and posterior hair whorl (1).

Forehead. High (sloping) forehead (43), flat supraorbital ridge (19), narrow bifrontal diameter (5), low frontal hairline (2), low (small) forehead (2), and prominent glabella (1) were present.

Eyes. Blepharophimosis (60) and ptosis (53) were usually present. Other minor facial anomalies include telecanthus (35), hypertelorism (27), scant eyebrows (20), upslant of palpebral fissures (15), downslant of palpebral fissures (6), epicanthus (15), arched eyebrows (2), hypotelorism (1), and a prelobular mass of the cheek (1).

Nose. Broad nasal bridge (31), prominent round tip (20), flat nasal bridge (16), large long nose (13), broad tip (11), anteverted nostrils (10), "abnormal" (6), short nose (3), long philtrum (3), flat philtrum , prominent nose (2), hypoplastic alae nasi (1), beak-shaped (1), and parrot-like (1) were present.

We think that a prominent round tip of the nose, noted in 17 of our 34 cases, is especially characteristic of the Dubowitz syndrome at a younger age, but was described previously in only three cases.

Ears. Apparently low-set (24), "abnormal" or "dysplastic" ears (19), posteriorly angulated (15), large and prominent (13), simple (9), large (6), small (5), hypoplastic helices (4), anteverted auricle (3), prominent (2), lack of antihelix (2), prominence of lower antihelix (2), hearing loss (2), forward-set (1), folded helix (1), hypoplastic tragus (1), right ear fistula (1), cup-shaped (1), and right preauricular fistula (1) were present.

Mouth. Large mouth (16), and small mouth (4) were present.

Lips. Flat philtrum (8), thin vermilion border of the upper lip (6), and long upper lip with prominent philtrum (3) were present.

TABLE III. Congenital Heart Defects

	Reported cases	Present cases	Total cases
VSD	3	2	5
PDA	3	1	4
ASD	0	2	2
CoA[a]	1	0	1
Mitral valve prolapse	1	0	1
"Innocent murmur"	1	7	8
"Heart murmur"	3	0	3
Others	0	2[b]	2

[a]Coarctation of aorta.
[b]Unexplained attack of tachycardia, small heart valve?

Palate. High (narrow) palate (30), submucous cleft palate (11), cleft palate (11), cleft uvula (9), and big adenoid and tonsils (1) were present. Submucous cleft palate is common and early detection is recommended strongly for prophylaxis of middle ear infections.

Chin. Micrognathia (81), and prognathism (1), narrow chin (1), and Robin sequence (1) were present.

Neck. Short (3), webbed (2), and long (1) were present.

Ocular Manifestations

Ocular problems occurred in 31 patients. They included strabismus (13), esotropia (5), microphthalmia (3), myopia (3), hyperopia (2), iris coloboma (2), nystagmus (1), anisocoria (1), megalocornea (1), iris hypoplasia (1), paresis (1), poor vision (1), astigmatism (1), blue sclerae (1), and deep optic nerve cupping and immature retinal vessels (1).

Funduscopic abnormalities included unusually tortuous retinal vessels [Opitz et al., 1973; Majewski et al., 1975], venous engorgement, pigmentary dysplasia [Opitz et al., 1973], hypopigmentation [Müller et al., 1978], albinotic fundi and increased vascular tortuosity [Opitz et al., 1973], prominence of disks [Majewski et al., 1975], and diffuse border of the optic disc [Borkenstein and Falk, 1978]. The electroretinogram was "slightly abnormal" in two cases reported by Opitz et al. [1973]. Severe eye involvement such as iris coloboma [Stoll et al., 1980; our case H.B.] is rare. Stoll et al. [1980] reported on a boy with bilateral iris coloboma. On the right there was a large coloboma of the posterior pole involving the macula; on the left there was an inferior chorio-retinal coloboma with intact macula. Guarniere et al. [1987] reported myopic chorioretinopathy. Orrison et al. [1990] described small fibrous bands extending from the vitreous to the posterior portion of the lens, and a "fan" of retina and vessels coming forward from the optic nerve centrally, representing a malformation of the retina and incomplete development and resorption of the primary vitreous posteriorly.

Dental Manifestations

Tooth problems (anomalies) were noted in 41 cases: delayed eruption (11), caries (8), crowded teeth (6), microdontia (4), malocclusion (4), malaligned (irregular) (3), diastema (2), conical (2), oligodontia (2), macrodontia (2), missing upper central incisors (1), fused (1), doubled (1), bifid incisors (1), rotated lower incisors (1), and incomplete true fusion of the primary right mandibular canine and first molar (1).

Cutaneous Manifestations

Sparse or thin hair and eczema were the most prominent cutaneous manifestations and were noted in 58 and 59 cases, respectively. Eczema was not observed in 42 cases. The site of involvement varied from the entire body except face (3), to a limited area of the body: face (11), elbow-flexures (6), popliteal fossa (5), neck (2), gluteal areas (2), scalp (1), trunk(1), "extensor area" (1), arms and legs (1), hands (1), and perianal area (1). Age of appearance ranged from 1 month (2) to 1½ month (1), 1 year (1), 2 years (1), and "infancy" (2).

Chronic severe eczema with intense itch was associated with excoriation, lichenification, and crusting. At times these raw, weeping, and/or crusted and intermittently infected areas covered most of body and the child was "miserably unhappy, ill tempered and severely hyperactive." The eczema often clears by age 2 to 4 years. It occasionally lasts after infancy, and in some cases into adult life. Topical medication including hydrocortisone cream is effective in some cases [Dubowitz, 1965; Grosse et al., 1971; Stoll et al., 1980; Vieluf et al., 1990], but ineffective in others [Wilroy et al., 1978, our case S.G.]. Dietary modification may be helpful in alleviating the eczema [Hochreutener et al., 1990]. In severe cases, sleep may be disturbed through the night [Hansen et al., 1995].

Other skin manifestations included dry skin (9), reduced subcutaneous fatty tissue (7), photosensitivity (5), hyperpigmentation (5), pigmented nevi (5), capillary hemangioma (4), seborrheic dermatitis (4), erythema (3), cutis marmorata (3), hyperkeratosis (2), diastasis recti (2), café-au-lait spot (2), umbilical hernia (2), congenital lymphedema (1), edema of feet (1), vascular marking (1), accessory nipple (1), hypotrichosis (1), atopic dermatitis (1), keloid scar (1), pityriasis (1), hypopigmentation (1), subcutaneous lymphangioma (1), and retarded wound healing (1).

Gastro-Intestinal Manifestations

Feeding difficulties during the neonatal period and infancy are common and are characterized by regurgitation, vomiting, and occasional projectile emesis. Vomiting occurred in 24 cases. Since these symptoms are related mostly to gastroesophageal reflux, and rarely to vascular abnormality [Orrison et al., 1980], a search for the underlying cause is recommended. Gastroesophageal reflux was demonstrated in five cases [Mathieu et al., 1991; our cases B.B., R.H.]. In fact, gastrostomy was performed in our case R.H. Chronic diarrhea and constipation were also prominent manifestations and observed in 15 and 13 cases, respectively. Congenital constipation associated with anal stenosis was reported in two cases [Ilyina et al., 1990]. Constipation was noted in five patients. Flatulence with severe constipation was noted in one patient [Majewski et al., 1975], rectal prolapse in three; anal stenosis in three [Ilyina and Lurie, 1990] and hiatal hernia in one patient [Mathieu et al., 1991].

Skeletal Manifestations

Skeletal abnormalities involved limbs more prominently than other parts of the body.

Skull. Large anterior fontanelle (2), delayed closure of the cranial sutures (1), unusually pointed symphysis of the mandible (1), and stenosis of the external auditory canal (1) [Castro-Gago et al., 1981] were present.

Hands. Fingers. Clinodactyly of the 5th fingers (48), short fingers (brachydactyly)(9), polydactyly (3), cutaneous syndactyly of fingers (2), nail hypoplasia (2), clinodactyly of the 2nd fingers (1), short metacarpals (1), radially deviated 5th fingers (1), ulnarly deviated 3rd fingers (1), overlapping fingers (1), mild hypertrophy of the interphalangeal joints (1), and small hands (1) were present.

Thumbs. Broad thumb (3), camptodactyly (3), proximal thumb (2), finger-like thumb (1), right bifid thumb with separate nails (1), hypoplastic thumb (1), and adducted thumbs (1) were present.

Feet. Cutaneous syndactyly of toes 2 and 3 (22), club foot (pes planovalgus, pes equinovalgus) (11), flat feet (pes planus) (10), broad first toes (8), nail absence or hypoplasia (6), small feet (5), overlapping (crowded) toes (5), diastasis of 1st and 2nd toes (2), cutaneous syndactyly of toes 3 and 4 (2), short 5th toes (2), short toes (2), cutaneous syndactyly of toes 4 and 5 (1), wide 2nd toe (1), short 1st metatarsals, brachymetatarsy (1), metatarsus varus (1), and adducted metatarsals (1) were present. Considering the frequencies of distal limb involvement it is remarkable that to date apparently no metacarpophalangeal profile analysis has been done in the Dubowitz syndrome.

Joints. Hyperextensible joints were noted in 13 cases: all joints were involved in 2 cases, others included finger joints (2), elbows and knees (1), knees (1); genu valgum was present in one case. Osgood-Schlatter disease was present in one case. Chest: Pectus excavatum (4), pectus carinatum (2), and rib synostosis (1) were present.

Hips. Hip "dysplasia" (4), congenital dislocation of the hips (2), and coxa valga (1) were present.

Vertebrae. Sacral (pilonidal) dimple (10), scoliosis (5), spina bifida occulta (2), sacral cleft (2), "positional" kyphosis or hyperlordosis (2), mild "dysplasia" of a cervical vertebral body (1), prominence of the lower portions of the sacrum (1), "dysplastic" cervical vertebrae (1) were present.

The patient reported first by Grosse et al. [1971] and later by Hansen et al. [1995] had many other skeletal abnormalities. They included narrowed T12-L1 interspace, unusual posterior angulation at S5, leg length discrepancy, asymmetric femoral condyles, flat plateau of the tibia, and absence of the anterior cruciate ligaments.

Bone age. Bone maturation, studied in 51 cases, was retarded in 37 (72.5%), normal in 13, and advanced in one.

Cardiovascular Manifestations

Congenital heart defects were diagnosed in 13 children (Table III). These included ventricular septal defect (5) [Küster and Majewski, 1986; Kondo et al., 1987; Benso et al., 1992; our case R.Y., M.S.], one with spontaneous closure [Kondo et al., 1987], and another requiring surgical closure [Benso et al., 1992]; patent ductus arteriosus (4) one of which was closed by the administration of indomethacin [Vieluf et al., 1990], one closing spontaneously [Lerman-Sagie et al., 1990], and two requiring surgical closure [Mathieu et al., 1991; our case B.W.]; atrial septal defect(2) (our case A.R., K.S.); coarctation of the aorta [Shuper et al., 1986]; mitral valve prolapse [Lyonnet et al., 1992]. An innocent murmur was reported in eight children [Grosse et al., 1971 and in six of our cases M.C, L.B., L.G., C.K, M.N., J.H., and C.M.]. A heart murmur not otherwise specified was noted in three cases [Orrison et al., 1980; Küster and Majewski, 1986; Kukushkina et al., 1990].

Unexplained attacks of tachycardia were noted in one of our patients (E.S.). Abnormal ECG findings indicating right ventricular hypertrophy, were documented in two cases [Grosse et al., 1971; Opitz et al., 1973] and right axis deviation in another [Kukushkina et al., 1990]. Anomalies of coronary vessels, an atresia lusuria, and a right descending aorta were reported in the case of Küster and Majewski [1986].

Urogenital Manifestations

Male. Genitourinary abnormalities occurred in 32 of 62 males (51.6%): cryptorchidism (26), inguinal hernia (11), hypospadias (10), small testes (6), small penis (4), hypoplastic genitalia (3), hypoplastic scrotum (1), and bifid scrotum (1).

Females. Three of twenty-four female patients had genital abnormalities: hypoplastic genitalia (2), hypoplasia of the clitoris and labia minora (1), hypoplastic labia majora (1), and partial vaginal septum (1).

Kidney. Kidney problems were noted in four cases: vesicoureteral reflux (3), hydronephrosis (1), later enuresis (1), and "mass on the right kidney" (1) (our case L.G.).

Neurological Manifestations

Neurological problems were noted in 25 cases. Thirteen patients had seizures [Müller et al., 1978; Wilroy et al., 1978; Orrison et al., 1980; Wilhelm and Méhes, 1986; Küster and Majewski, 1986; Vieluf et al., 1990; Benso et al., 1992; Hansen et l., 1995; our three cases B.B, L.R, R.H], and one with breathholding spells (our case J.L.). Grand mal seizures were noted in two individuals [Küster and Majewski, 1986; Hansen et al., 1995]. Also noted were muscular hypotonia (11) [Majewski et al., 1975; Küster and Majewski, 1986; Shuper et al., 1986; Chrzanowska and Krajewska-Walasek, 1987; Guarniere et al., 1987; our four cases (B.B., H.C., J.F., M.L)]; muscular hypertonia (7) [Shuper et al., 1986; Kukushkina et al., 1990; Mathieu et al., 1991; our case M.N.]; hypertonicity of the legs (6) [Grosse et al., 1971; Küster and Majewski, 1986; Shuper et al., 1986; Mathieu et al., 1991]; migraine headaches (3) [Orrison et al., 1980; Hansen et al., 1995; our case J.H.]; presence of Babinski sign (2)[Opitz et al., 1973; Chrzanowska and Krajewska-Walasek, 1987]; meningomyelocele and internal hydrocephalus [Berthold et al., 1987]; hydrocephalus [Kukushkina et al., 1990]; truncal ataxia [Levin et al., 1987]; hyperactive deep tendon reflexes [Opitz et al., 1973] or hypoactive deep tendon reflexes [Shuper et al., 1986], and paralysis of the bladder and anus [Küster and Majewski, 1986].

Abnormal EEG findings included spike waves in the temporal areas (our case M.L.), bioccipital dysrhythmia [Opitz et al., 1973], slow rhythm in the parieto-temporo-occipital region [Walter, 1980], and diffuse slowing in the right hemisphere [Orrison et al., 1980]. Abnormal brain CT findings included dilated ventricle (3) [Mathieu et al., 1991; Gomirato et al., 1992; our case No.26], asymmetric ventricles in one of our cases (R.H.), decreased density in the right frontal region [Orrison et al., 1980]. Magnetic resonance imaging (MRI) showed brain atrophy in one case (R.Y.). Absent visual evoked response in the left was noted in one case [Orrison et al., 1980]. On the other hand, EEG was normal in 14 cases [Grosse et al, 1971; Opitz et al., 1973; Majewski et al., 1975; Borkenstein and Falk, 1978; Müller et al., 1978; Wilroy et al., 1978; Walter; 1980; Guarniere et al., 1987; Vieluf et al., 1990; Benso et al., 1992; our case R.H.]. Electromyogram (EMG) was normal in five cases [Majewski et al., 1975; Castro-Gago et al., 1981; Levin et al., 1987]. Nerve conduction velocity was normal in three cases [Majewski et al., 1975; Küster and Majewski, 1980].

Behavior Problems

The voice is characteristically high-pitched or hoarse, and occasionally described as "squeaky" [Grosse et al., 1971] or "cat-cry" like [Wilroy et al., 1978]. The voice was high-pitched in 38 and hoarse in 11 cases. Hypernasal voice was noted in five cases with velopharyngeal insufficiency in two cases [Lerman-Sagie et al., 1990; Hansen et al., 1995].

Behavior problems were noted in 52 patients. Hyperactivity is the most characteristic behavior problem and has been reported in 50 cases. It is very difficult to manage, and in some cases interferes with sleep. Other behavior problems were cited less frequently; they included "shyness" (6) [Grosse et al., 1971; Opitz et al., 1973; Majewski et al., 1975; Wilroy et al., 1978; Guarniere et al., 1987], short attention span (5) [Grosse et al., 1971; Wilroy et al., 1978; Parrish and Wilroy, 1980; Wilhelm and Méhes, 1986; Shuper et al., 1986], "aggressiveness and agitation" [Mathieu et al., 1991], stubbornness [Grosse et al., 1971], carelessness and poor compliance [Lyonnet et al., 1992]. Parrish and Wilroy [1980] reported that a patient may be "hyperactive, moody, and sensitive to criticism," or may refuse to accept food, display impulsivity, and may be a "picky eater" or "bed wetter."

Behavior patterns in our cases were analyzed in 11 cases using the questionnaire provided by the parents with detailed behavior description. In one case detailed clinical information was obtained without a questionnaire. This information disclosed characteristic behavior patterns all the more impressive since the data were provided by the parents without prompting or interpretation by professionals.

Fascinations included "music" (3 cases); "watching ceiling fans" (2); "dancing" (2); "vibrations" (2); "toys" (2); "needs freedom" (1); "noises" (1); "needs to be alone" (1); "repetition of phrases and noises" (1); "bounces on her couch for hours" (1); "watching rolling T.V. credits" (1); "twirls her hair 23 of 24 hours" (1); "feeling wall and soft fabrics" (1). Parents also noted selfishness; "temper tantrums" (stomps feet, yells etc.)(3); "angry outbursts" (1). To get attention a patient may "bite" (1), "pull hair" (1), or "slap himself" (1). Other descriptions included "screaming" (2); "silliness" (1); "crying" (1); "whining" (1); "touching" (1); "kicking" (1); "pushing" (1); "some excitable/giggly episodes at school when he is hard to control" (1); "tries to sleep with parents" (1); "wants to be the center of attention" (1); "when upset folds all his fingers over each other and his head goes down" (1); enjoys "affection and physical contact and cuddling" (1). Dis-

likes included crowds (3); "loud noises" (3); "being alone" (1); "wind" (1); "ocean" (1); "a small enclosed area" (1); "autistic tendency" was described in one case.

Frequent Infections

Recurrent infections were common in Dubowitz syndrome patients (Table IV). At the moment it is unknown whether patients with the Dubowitz syndrome are unusually susceptible to infection because of some impairment of their immunological function. Recurrent infections occurred in 45 cases; without further description (30), repeated otitis media (22), urinary tract infection (14), upper respiratory infection (11), pneumonia (3), sinusitis (2), chronic rhinitis (2), ulcerative stomatitis (2), encephalitis (1), purulent dacryocystitis (1), croup syndrome (1), pertussis (1), mucositis (1), tonsillitis (1), and enteritis (1). Hearing loss secondary to chronic otitis media or to Gentamycin® was noted in nine patients. Periodic hearing assessment is recommended in patients with frequent otitis media.

Allergy

"Allergic status" was noted in 22 cases: bronchial asthma (11) and atopic dermatitis (4), and 13 with other allergy including food, pollen, dust, milk, or molds. Allergies occurred in 15 of our 36 patients. RAST was positive in one case each for *Dermatophagoides pteronyssimus* [Paradisi et al., 1994], and for house dust [Vieluf et al., 1990].

History of Surgical Procedures

A history of surgical treatment was obtained in 33 cases: orchidopexy (10), ptosis (7), otitis media (6), herniorrhaphy (6), heart surgery (6), blepharophimosis (4), tonsillectomy (3), strabismus (3), adenoidectomy (2), club foot (2), cleft palate (2), or submucous cleft palate repair (1), tongue-tie (1), myringotomy (1), hypospadias (1), rectal prolapse (our case R.H.), vocal cord cyst and removal of cartilage from the nose (our case J.A.), meningomyelocele [Küster and Majewski, 1986], chronic dacryostenosis [Grosse et al., 1971], velopharyngeal insufficiency [Lerman-Sagie et al., 1990; Hansen et al., 1995], subcutaneous lymphangioma [Lyonnet et al., 1992], aberrant subclavian artery [Orrison et al., 1980], bilateral tubal ligation [Hansen et al, 1995], and polydactyly [Kukushkina et al., 1990].

TABLE IV. Frequent Infections

	Reported cases	Present cases	Total cases
Frequent infections[a]	14	16	30
Otitis media	8	14	22
Upper respiratory	8	3	11
Pneumonia	1	2	3
Urinary tract	10	4	14
Others[b]	11	2	13

[a]No further description.
[b]sinusitis (2), chronic rhinitis (2), ulcerative stomatitis (2), encephalitis (1), purulent dacryocystitis (1), croup syndrome (1), pertussis (1), mucositis (1), tonsillitis (1), enteritis (1).

COMPLICATIONS

Velopharyngeal insufficiency. Velopharyngeal insufficiency associated with submucous cleft palate has been reported twice [Lerman-Sagie et al., 1990; Hansen et al., 1995]. In patients with submucous cleft palate and hypernasal speech, a cineradiographic evaluation of the soft palate is recommended [Lerman-Sagie et al., 1990]. Deletion at 22q11 should be checked in these patients.

Vascular abnormalities. Orrison et al. [1980] reported on two cases with vascular abnormalities. A 3½-year-old girl, who developed acute left arm weakness and vomiting with subsequent seizure-like episodes, nausea, vomiting, and severe headache, was diagnosed as having hemiplegic migraine. Arteriography showed complete occlusion of the right internal carotid artery. The other 2-year-old girl had an aberrant subclavian artery which compressed the esophagus resulting in severe dysphagia and frequent vomiting which resolved after ligation.

Hypoparathyroidism. Lerman-Sagie et al. [1990] reported on a 6-year-old boy with neonatal hypoparathyroidism from which he recovered in 2 months after the administration of calcium gluconate and vitamin D; this redeveloped at age 6 years. He also had velopharyngeal insufficiency. Deletion at 22q11 should be checked in this patient.

Hematological and malignant disorders. A propensity to hematological and malignant disorders has been reported (Table V). It is noteworthy that in some cases they were associated with immunological abnormalities. Gröbe et al. [1983] reported on a 6-year-old girl, previously reported by Opitz et al. [1973] (case 3), who developed acute lymphoblastic leukemia at age 6¾ years, and died 16 days after admission. Sauer and Spelger [1977] reported on two sisters, one with hypogammaglobulinemia and neuroblastoma, and the younger with complete IgA deficiency and malignant lymphoma. The younger sister had an elevated level of vanillylmandelic acid (VMA), but a search for neuroblastoma by urography, chest X-ray film, and bone marrow aspiration failed to disclose neuroblastoma. One year after chemotherapy the VMA level returned to normal. A right upper mediastinal shadow appeared at age 6 years and was diagnosed as germinal blastic sarcoma or diffuse germinal blastoma. She died of pneumonia after radiation. Walters and Desposito [1985] reported on two sibs, cases 5 and 6 previously reported by Opitz et al. [1973], one of whom, the 12-year-old brother, had leukopenia, foci of bone marrow hypocellularity, and several premorbid signs of aplastic anemia; the 10-year-old sister developed aplastic anemia. Berthold et al. [1987] re-reported the patient of Nöll-Gröbe and Fuhrmann [1983], who developed pancytopenia at age 3 years, and died of severe anemia and pulmonary hemorrhage at age 3½ years. Belohradsky et al. [1988] also reported on a 16-year-old boy with non-Hodgkin lymphoma with a leukemic course. Ilyina and Lurie [1990] reported on two sibs with severe hypoplastic anemia. Thuret et al. [1991] reported on two sisters who had repeated infections and recurrent ulcerative stomatitis, leukopenia (elder sister), and recurrent neutropenia

TABLE V. Hematological and Malignant Disorders*

	Sex	Age at diagnosis	Age at death	Immunoglobulins A	M	G	Author
Leukopenia	F	7	alive	–	↑	n	Thuret et al. [1991]
Agranulocytosis	F	4	alive	↓	↑	↓	Thuret et al. [1991]
Pancytopenia	M	3	3.5	n	n	n	Berthhold et al. [1987]
	F	2	alive	?	?	?	Anyane-Yeboa [1995]
Aplastic anemia	F	10	alive	n	n	n	Walters and Desposito [1985]
	M	12	alive	?	?	?	Walters and Desposito [1985]
	F	6 9/12	?	?	?	?	Ilyina and Lurie [1990]
	M	4 3/12	?	?	?	?	Ilyina and Lurie [1990]
Acute lymphoblastic leukemia	F	6	6	–	n	n	Gröbe et al. [1983]
Non-Hodgkin lymphoma	M	16	?	n	n	n	Belohradsky et al. [1988]
Malignant lymphoma	F	6	6	–	n	n	Sauer and Spelger [1977]
Neuroblastoma	F	3	3	[a]	[a]	[a]	Sauer and Spelger [1977]

*–, complete deficiency; ↓, low; n, normal; ?, not described; [a], hypogammaglobulinemia.

and agranulocytosis (younger sister). Both had bone marrow abnormalities; immunoglobulin studies demonstrated complete IgA deficiency with normal IgG and elevated IgM in the younger sister, and low values of IgG and IgA with elevated IgM in the elder sister. Both had "chromosome instability".

Iron deficiency anemia was noted in four cases [Opitz et al., 1973; Majewski et al., 1975; Ilyina and Lurie, 1990]. Easy bruisability with normal coagulation studies was noted in one of our cases (J.H.). A 2-year-old girl (C.M.) referred by Dr. K. Anyane-Yeboa had episodes of viremia accompanied by pancytopenia and bone marrow hypoplasia with absent megakaryocytes. She had no spontaneous or DEB-induced chromosome breakage in her T-lymphocytes; and sister chromatid exchange rate was normal. Initial chromosome analysis in a bone marrow specimen was normal but a repeat bone marrow specimen taken a few months later documented extensive chromosome breakage.

Immunological Study

As noted above, abnormal immune globulin levels were reported (Table V), although normal levels were also reported [Opitz et., 1973; Majewski et al., 1975; Stoll et al., 1980; Berthold et al., 1987; Belohradsky et al., 1988; Lerman-Sagie et al., 1990; Thuret et al., 1991; Lyonnet et al., 1992]. In some of cases, elevated IgM levels may be the consequence of frequent infection. A high IgE level was reported once [Hochreutener et al., 1990]. T cell function was normal in four cases [Stoll et al., 1980; Berthold et al., 1987; Belohradsky et al., 1988; Lerman-Sagie et al., 1990], and low T_3 and T_4 T-cell fractions were observed in one case [Belohradsky et al., 1988].

Cytogenetic Analysis

Results of chromosome analyses, performed in 77 patients, were apparently normal. High resolution banding analysis performed in two case was also normal [Levin et al., 1987; our case No.26]. Spontaneous breaks were slightly increased in one of two sibs, and normal in the other [Walters and Desposito, 1985]. A high breakage rate after clastogenic stress was observed in two sibs who showed leukopenia and recurrent neutropenia and agranulocytosis [Thuret et al., 1991]. On the other hand, no increased breakage was found in six cases [Walters and Desposito, 1985; Berthold et al., 1987; our cases No.26, H.I., C.M.]. Results of sister chromatid exchange (SCE) studies performed in five cases were normal [Wilhelm and Méhes, 1986; Berthold et al., 1987; our cases No.26, H.I., C.M.]. Fluorescence in situ hybridization (FISH) analysis revealed no deletion at 22q11 in one case (H.I.).

Dermatoglyphics

Abnormal dermatoglyphic patterns were documented in 30 cases (Table VI): preponderance of ulnar loops (14), abnormal flexion creases (8), interdigital loop patterns (8), distal axial triradii (5), hypothenar patterns (5), preponderance of whorls (3), absence of interdigital triradius c (2) or d (1), ridge dysplasia of the proximal palm (1), low total ridge count (1), and tibial loop in the hallucal areas (1). A quantitative dermatoglyphic study in the Dubowitz syndrome is lacking to date.

Laboratory Examinations

The results of routine biochemical and metabolic screening were normal in most cases, including erythrocyte sedimentation rate, blood counts, renal and liver function tests, serum electrolytes, serum lipids,

TABLE VI. Dermatoglyphic Findings

	Reported cases	Present cases	Total cases
Abnormal	27	3	30
Preponderance of ulnar loops	11	3	14
Abnormal flexion creases	8	0	8
Interdigital loop	5	3	8
Distal axial triradius	2	3	5
Hypothenar pattern	5	0	5
Preponderance of whorls	3	0	3
Absence of c triradius	0	2	2
Absence of d triradius	0	1	1
Ridge dysplasia	1	0	1
Low total ridge count	1	0	1
Tibial loop in hallucal areas	1	0	1

blood gases, urinalysis, urinary steroids, blood and urine amino acid chromatography, serum creatine phosphokinase, and aldolase and transaminase levels [Dubowitz, 1965; Opitz et al., 1973; Wilroy et al., 1978; Fryns et al., 1979; Castro-Gago et al., 1981; Walters and Desposito, 1985; Shuper et al., 1986; Kondo et al., 1987; Kukushkina et al., 1990; Lyonnet et al., 1992; Benso et al., 1992; Paradisi et al., 1994]. Abnormal findings included low hemoglobin level [Grosse et al., 1971], microcytic anemia [Opitz et al., 1973; Majewski et al., 1975], macrocytic anemia and severe thrombocytopenia [Berthold et al., 1987], eosinophilia [Majewski et al., 1975], and mild elevation of serum creatine phosphokinase and lactic dehydrogenase [Levin et al., 1987]. Urinary excretion of lysosomal enzymes was normal [Majewski et al., 1975]. TORCH test results were all *negative [Opitz et al., 1973; Castro-Gago et al., 1981; Shuper et al., 1986; Guarniere et al., 1987; Lerman-Sagie et al., 1990]*. Serum vitamin A [Dubowitz, 1965; Majewski et al., 1975], C and E [Majewski et al., 1975], and B_{12} and folic acid [Berthold et al., 1987] levels were normal. Results of endocrine surveys were also normal, including pituitary, thyroid function tests, adrenal cortical function tests, and growth hormone levels [Grosse et al., 1971; Opitz et al., 1973; Majewski et al., 1975; Wilroy et al., 1978; Castro-Gago et al., 1981; Shuper et al., 1986; Guarniere et al., 1987; Kondo et al., 1987; Lyonnet et al., 1992]. Levin et al. [1987] reported an elevated level of thyroid-stimulating hormone (TSH) with normal values of β-TSH, α-subunit human chorionic gonadotropin (hCG), free T4, T4RIA, T3RIA, TBG, and thyroid antibodies. Thyroid replacement therapy showed appropriate suppression of TSH. Somatomedin levels were normal in one case [Levin et al., 1987], and reduced in one case [Gomirato et al., 1992]. Results of sweat tests were normal [Wilroy et al., 1978; Gomirato et al., 1992].

Follow-Up Data

An old-looking appearance or premature aging was described [Fryns et al., 1979; Lyonnet et al, 1992]. On the other hand, a 30-year follow-up report of the patient (J.H.) first published by Grosse et al. [1971] described her as appearing younger than her chronological age [Hansen et al., 1995].

Periodic follow-up will disclose speech, dental, and hearing abnormalities as described by Moller and Gorlin [1985].

Familial Occurrence

The cause of the Dubowitz syndrome is unknown, but is presumed to represent the homozygous state of an autosomal recessive mutation. Familial occurrence was found 15 times in a total of 141 patients. Affected sibs in nine families included a brother and sister [Grosse et al., 1971; Opitz et al., 1973; Wilroy et al., 1978; Walter, 1980; Wilhelm and Méhes, 1986; Ilyina and Lurie, 1990; Kukushkina et al., 1990; Mathieu et al., 1991], in two brothers [Wilroy et al., 1978; Castro-Gago et al., 1981], in three sisters [Dubowitz, 1965; Sauer and Spelger, 1977; Thuret et al., 1991]; in one family three sibs were affected [Winter, 1986]. One hundred ten cases were sporadic. In 2 of 15 familial cases the parents were consanguineous (first cousins) [Opitz et al., 1973; Winter, 1986]. One set of concordant monozygotic twins is known [Wilroy et al., 1978]. In our cases one family has had dizygotic (unlike sex) twins with only one twin affected. One affected and one or more normal sibs were present in 40 families (103 individuals) of which 42 were affected and 61 were normal. Thus, the ratio of affected to total sibs without ascertainment correction was 0.40.

Affected sibs born to phenotypically normal parents, the presence of parental consanguinity, concordantly affected monozygotic twins, and an equal number of affected males and females are data compatible with autosomal recessive inheritance. This condition is probably much more common than suggested by the literature. In one case there was a suggestion of dominant inheritance. Méhes [1990] reported on an 8-year-old girl with the Dubowitz syndrome whose mother had microcephaly, short stature, telecanthus, epicanthus, thin hair, clinodactyly, and a borderline I.Q (77).

DISCUSSION

The Dubowitz syndrome is a multiple congenital anomalies (MCA)/mental retardation (MR)/growth failure condition with immune defect predisposing to allergies and eczema, liability to blood dyscrasias (white, red, pancytopenia), hematologic malignancies, and neuroblastoma. The pathogenesis is unknown; however, a metabolic and/or DNA repair defect must be ruled out. The phenotype suggests mosaic pleiotropy, i.e., intracellular action of the mutant genotype at various times during pre- and post-natal development. The phenotypic variability appears to be extraordinarily broad suggesting action of many modifying genetic or epigenetic factors; however, within a sibship the phenotype tends to be similar. At the moment, prenatal diagnosis is not reliable; there is a suggestion that some carriers may show mild manifestations. However, it is important to screen carefully 1st and 2nd degree relatives for evidence of increased predisposition to neoplasia.

Some of the findings in the Dubowitz syndrome are similar to those of the fetal alcohol syndrome. They include pre- and post-natal growth retardation, mild to severe mental retardation, microcephaly, and similar minor facial anomalies. However, lack of history of prenatal exposure to ethanol, and an overall pattern of clinical manifestations different from that of the fetal alcohol syndrome make the distinction easy [Opitz et al., 1973]. Other important differential diagnostic considerations include Bloom syndrome and Fanconi anemia; patients with these condition may also manifest growth and mental retardation, skin abnormalities (not eczema), and hematological and immunological abnormalities. However, facial appearance and other clinical manifestations are different from those seen in the Dubowitz syndrome. Studies on chromosome instability have been performed infrequently, and the association of the Dubowitz syndrome with chromosome instability remains unresolved.

Regular, long-term follow-up of patients with the Dubowitz syndrome is recommended.We suggest regu-

lar study of 1) growth: plot carefully; consideration of treatment with growth hormone or anabolic steroids may be discussed with pediatric endocrinology consultant; 2) health status including regular physical examination, urinalysis, and complete blood count; 3) speech and dental development, and hearing, especially in those who have had multiple middle ear infections; 4) behavior/neurologic problems; 5) D.Q./I.Q.: Denver developmental scale and other formal testing; 6) surgical needs: repair of craniofacial, limb, or urogenital anomalies; 7) surveillance for hematological and malignant (mostly neuroblastoma) disorders; and 8) educational programs appropriate for individual patients.

ACKNOWLEDGMENTS

We thank Drs. K. Anyane-Yeboa, J. Belmont, T.R. Gollop, G. Hoyme, B. Kousseff, H.H. Kramer, J.J. Lambert, S.W. Levin, S.M.E. Lewis, E. Magenis, E. Pergament, C. Schrander-Stumpel, J.B. Sidbury, and E.M. Zorn for referring patients. We also thank Mrs. J. Kerns, Dubowitz Syndrome Parent Support Group, for her collaboration, and Drs. V. Bracho Mosquera, I. Fernandez De Bracho, and G. Rudenskaya for their kind help.This work was supported in part by Grant-in-Aid from the Ministry of Education, Science and Culture of Japan (M.T.) and by a Grant-in-Aid from the Ministry of Health and Welfare of Japan (M.T.).

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APPENDIX A (CLINICAL REPORT)

J.F., a 2½-year-old boy, was born at term after a normal vaginal delivery with a birth weight of 3,402 g. Length and head circumference were not available. Apgar scores were 9 and 10. Unusual facial appearance was noted from birth. He had hypospadias and cryptorchidism. He had a cyanotic episode on the 2nd day. He sat at 6 months. Developmental assesment at the age of 1 year showed him to have mild gross motor delay. His other development appeared normal though he had some expressive language delay. He had had an orchidopexy and hypospadias repair at age 11 months. Chromosomes were normal. At age 1⁹⁄₁₂ years, he had right otitis media which responded well to antibiotics. He did not have eczema, sparse hair, vomiting, or diarrhea from birth. With respect to growth he had been on the 25th–50th centile (height), 25th–50th centile (weight),and 50th centile for OFC.

At 2½ years, he weighed 13.8 kg (50th centile), measured 93 cm (50th centile), and had an OFC of 49.8 cm (50th centile). He had a right facial weakness with mouth and eye remaining open on the right side. He had sloping forehead, short palpebral fissures, ptosis, epicanthic folds, broad nasal bridge, prominent round tip of the nose, and high-arched palate (Fig. 1). His ears were posteriorly angulated. The helix was unfolded, and tragus, antitragus and earlobe were hypoplastic. He had micrognathia. His index fingers overlapped the 3rd fingers. He had mild syndactyly of the 2nd and 3rd toes bilaterally, corrected hypospadias and orchidopexy scars.

APPENDIX B (INTERNATIONAL DUBOWITZ SYNDROME REGISTRY PROTOCOL)

We have prepared a Dubowitz syndrome questionnaire for purposes of an international registry (Table VII) based in part on the Parent Questionnaire. We would be most grateful for information on new and follow-up data on known cases in order to get a much better idea of phenotypic spectrum and natural history. This will also make it possible to respond efficiently for further studies and to disseminate new information. We would like to collaborate with those who have studied familial cases in order to expedite mapping the gene(s).

TABLE VII. International Dubowitz Syndrome Registry Patient Questionnaire

Date: _____

A) Personal Data:
1) Patient name or code no.:_____
2) Ethnic background: _____
3) Date of Birth: _____ Age: _____ Sex: Male or Female
4) Age at Diagnosis: _____ (month/years)
5) Occurrence in sibs: + / - Reason for referral:
6) Number of normal sibs Family history:

B) Pregnancy Data:
1) Gestational age: _____ (wks) G ___ P ___ SA ___ IA ___
2) Fetal movement: decreased normal
3) Complication(s): _____

C) Delivery Data:
1) Presentation: Cephalic Breech C-section
2) Complication(s): _____

D) Birth Data:
1) Maternal Age: ___ Years Paternal Age: ___ Years
2) Consanguinity: + / -
3) Weight: (_____g) (_____ centile or SD) Length: (_____ cm)(_____ centile or SD)
Head circumference: (_____cm)(_____ centile or SD)
4) Apgar score: (___ - 1 minute) (___ - 5 minute)
5) Any problem(s) at birth: _____

E) Neonatal Data: ___ Respiratory problems ___ Feeding difficulties Other(s):_____

F) Growth & Development Data:
1) Age at last visit: _____ month/year(s)
2) Measurement at last visit: Weight: (_____ g)(_____ centile or SD)
Length: (_____cm)(_____centile or SD) Head circumference: (_____ cm)(___ centile or SD)
3) Milestones (what age?): _____ Roll over _____ Sit _____ Stand
_____ Walk _____ Speak first words
4) Psychomotor retardation: + / - Speech delay: + / -
a. IQ: Full Scale IQ ___ Verbal IQ ___ Performance IQ ___
b. DQ: ___
5) Current educational placement: _____
6) Behavior: ___ Abnormal ___ Normal ___ Hyperactivity ___ Shy ___ Angry Outbursts ___
Any Oddities: ___ Hate crowds ___ Loud Noises ___ Likes to feel vibration of music speakers, etc.
Other Oddities: _____

G) Health History: _____

H) Clinical Manifestations:
1) Craniofacial:
a. Skull: ___ Microcephaly ___ Dolichocephaly ___ Brachycephaly ___ Craniosynostosis
___ Narrow bifrontal diameter ___ Facial asymmetry Other(s)_____
b. Forehead: ___ Sloping (high) ___ Flat supraorbital ridge Other(s)_____
c. Eye(s): ___ Ptosis ___ Blepharophimosis ___ Epicanthus ___ Telecanthus
___ Hypertelorism ___ Scanty eyebrows ___ Arched eyebrows ___ Strabismus
___ Microphthalmos ___ Megalocornea ___ Iris hypoplasia ___ Coloboma
___ Hyperopia ___ Myopia ___ Esotropia ___ Fundus (___ Abnormal vein,
___ Tapetoretinal degeneration ___ Albinism Other(s) _____)
Other(s) _____
d. Nose: ___ Prominent ___ Broad nasal bridge ___ Flat nasal bridge ___ Long philtrum
___ Flat philtrum ___ Prominent round tip Other(s) _____
e. Ear: ___ Large ___ Prominent ___ Lowset ___ Posteriorly angulated ___
Hearing loss: ___ Mild ___ Moderate ___ Severe
Other(s) _____
f. Mouth: ___ Large ___ Small ___ Thin vermilion border of the upper lip
___ Cleft palate ___ Narrow (high) palate ___ Cleft uvula
Voice: ___ High pitched ___ Hoarse ___ Normal Other(s) _____
g. Chin: ___ Micrognathia ___ Prognathism Other(s) _____
h. Neck: ___ Short ___ Webbed
i. Other(s): _____
2) Teeth: ___ Malocculusion ___ Caries ___ Crowded ___ Malaligned ___ Doubled ___ Fused ___ Conical
___ Oligodontia ___ Microdontia ___ Macrodontia ___ Diastema ___ Enamel dysplasia
Other(s): _____
3) Skin: ___ Eczema (site _____) (Age of appearance ___ month/years)
(Age of disappearance ___ month/years) ___ Atopic dermititis ___ Seborrhoic dermatitis ___ Erythema
___ Hyperpigmentation ___ Hypopigmentation ___ Photosensitivity ___ Sparse(thin) hair ___ Dry skin
Other(s): _____
4) Urogenital: ___ Cryptorchidism ___ Hypospadias ___ Small testes ___ Inguinal hernia ___ Anal stenosis
___ Kidney problems (_____) Other(s): _____
5) G-I Tract: ___ Vomiting ___ Chronic diarrhea ___ Constipation ___ Rectal prolapse ___ Other(s): _____
6) Skeletal:
a. Hands: ___ Clinodactyly of 5th fingers ___ Short fingers ___ Broad thumbs
___ Proximal thumb ___ Camptodactyly ___ Nail hypoplasia
___ Cutaneous syndactyly of fingers ___ Polydactyly
Other(s): _____
b. Feet: ___ Club foot ___ Cutaneous syndactyly (toes 2-3) ___ Broad halluces (first toes)
___ Small feet ___ Flat feet ___ Crowded toes ___ Nail hypoplasia
Other(s): _____
c. Vertebrae: ___ Scoliosis ___ Spina bifida occulta ___ Sacral dimple Other(s): _____
d. Chest: ___ Pectus carinatum ___ Rib synostosis Other(s): _____
e. Joints: ___ Hyperextensible (site _____) Other(s): _____
f. Bone age: ___ Retarded ___ Normal
7) Congential Heart Defect: ___ Innocent murmur ___ ASD ___ VSD ___ PDA Other(s):_____
ECG findings: _____
8) Central Nervous System: ___ Seizure ___ Migraine CT findings _____
MRI findings _____ EEG findings _____
Other(s):_____
9) Frequent infections: ___ Otitis media ___ Upper respiratory ___ Pneumonia ___ Urinary tract
Other(s): _____
10) List of any surgery: ___ Orchidopexy ___ Herniorrhaphy ___ Tonsillectomy ___ Adenoidectomy ___ Ptosis
___ Heart surgery ___ Strabismus ___ Blepharophimosis ___ Otitis media (PE tube) ___ Hypospadias
Other(s): _____
11) Complication(s):
1. Allergy: ___ Bronchial asthma ___ Atopic dermititis ___ Food allergy (_____)
Other(s): _____
2. Hematological disorders: _____
3. Malignant disorders: _____
4. Other(s): _____
12) Examination(s):
1. Karyotype (___ G-banded, ___ high resolution banded)_____
Others: (example: breakage and SCE, etc.) _____
2. Immunoglobin levels (Ig G, A, M, E):
___ Abnormal (_____) ___ Normal ___ Not done
3. List of other abnormal findings: _____

Current Physician (address/telephone/FAX): _____

Please send completed questionnaire to: John M. Opitz, M.D., FDMG-FRB-Suite 229, 100 Neill Avenue, Helena, MT 59601

Rev. 10/95